947,643

# PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—C 07 c, d.

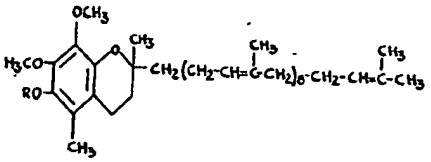
COMPLETE SPECIFICATION

## Substituted Chroman Compounds

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

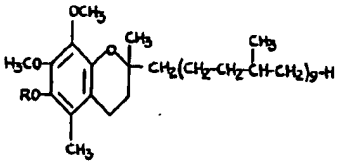
This invention relates to chroman compounds and methods of preparing them. More particularly, it is concerned with 2,5-dimethyl-2-[3¹-methyl-2¹-butenyl-octakis(3¹-methyl-2¹-butenylene)-methyl]-6-hydroxy-7,8-dimethoxy-chroman and 2,5-dimethyl-2 - (4¹,8¹,12¹,16¹,20¹,24¹,28¹,32¹,36¹ - nonamethylheptatricontanyl) - 6 - hydroxy-7,8-dimethoxy-chroman, acyl derivatives thereof, and methods of preparing these compounds.

The new chroman compounds of the present invention are represented by the formulas:



I

and

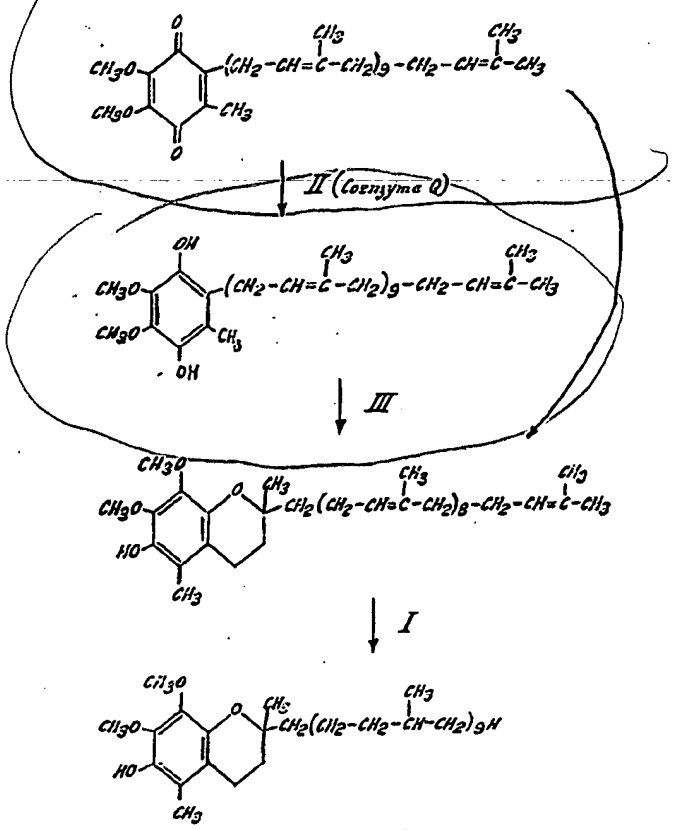


IV

where R is a hydrogen atom or an acyl radical. Compound I above is also referred to herein as the "chroman of Coenzyme $Q_{10}$."

The starting material for the preparation of the new chromans of the present invention is "Coenzyme Q", an essential quinone which is involved in respiratory metabolisms and has been discovered in heart mussle tissue as an effective part of the system of oxidative metabolism (Cf. Prof. David E. Green, in The Harvey Lectures, (1956—57), p. 177, Academic Press, New York; Crane, Hatefi, Lester and Widmer, Biochim. Biophys. Acta *25*, 220 (1957)). The processes by which coenzyme Q is converted to the new chromans of the invention can be illustrated structurally as follows:

[*Price 4s. 6d.*]




In accordance with one embodiment of the present invention, the starting material, Compound II or coenzyme Q, is heated under reduced pressure to produce Compound I or 2,5-dimethyl-2-[3¹-methyl-2¹-butenyl-octakis(3¹-methyl-2¹-butenylene)-methyl]-6-hydroxy-7,8-dimethoxychroman thus by-passing Compound III in the above scheme. Compound I is obtained when coenzyme Q is heated to a temperature in excess of about 250° C., preferably between 250—280° C. at about 1 to 10 microns pressure. Under these conditions, the desired product distils off and can readily be recovered in accordance with methods known in this art.

Pursuant to a further embodiment of the process, the chroman Compound I may also be prepared by following the first two steps of the main line of the reaction scheme viz. by first reducing the quinone Compound II to the corresponding hydroquinone III and then heating the hydroquinone in the presence of a suitable acid catalyst to a temperature in excess of about 50° C. to produce Compound I. The first step of this process comprising the reduction of the quinone compound can be carried out by a number of different procedures. Thus, the reduction can be effected by treatment with reducing agents, such as sodium borohydride, metal and acid combinations of sodium hydrosulphite. The second step of the reaction is carried out by heating the hydroquinone in the presence of a suitable acid catalyst such as *p*-toluene sulphonic acid, sulphuric acid and formic acid. Alternatively, the conversion of the hydroquinone to the chroman compound can be effected by heating the hydroquinone in the presence of a catalysing agent such as zinc chloride or stannous chloride. Generally, in carrying out this step of the process, it is desirably effected in the presence of a suitable solvent for the hydroquinone such as glacial acetic acid, dioxane and the like at a temperature of about 100° C.

In accordance with a preferred embodiment of the present invention which again

follows the first two steps of the main line of the reaction scheme, the chroman compound is most conveniently prepared by heating a solution of coenzyme Q in glacial acetic acid to reflux temperature, adding stannous chloride to it in an amount sufficient to convert the quinone to the hydroquinone III, and continuing the heating under reflux for sufficient time to complete the formation of the desired chroman compound I. The amount of stannous chloride used in this process should be sufficient to change the colour of the coenzyme Q solution from its original yellow-orange colour. Alternatively, in place of using glacial acetic acid in this process, other suitable solvents, boiling at about 100° C., such as dioxane, can also be used.

It will thus be seen that the invention provides three methods of producing Compound I viz:—

1. A process for producing a chroman of Coenzyme Q10 which comprises heating a compound of Formula II to effect internal cyclization and thereby obtain a compound of Formula I.
2. A process for producing a chroman compound which comprises reducing a quinone compound of Formula II to the corresponding hydroquinone and heating this hydroquinone in the presence of an acid catalyst to produce a chroman compound of Formula I.
3. A process for producing a chroman compound which comprises reacting a quinone compound of Formula II with stannous chloride at a temperature in excess of about 50° C. to product a compound of Formula I.

In accordance with a further embodiment of the invention, the chroman Compound I can be hydrogenated as shown in the last step of the reaction scheme to produce the corresponding polyhydro derivative, Compound IV. This reduction can be readily and conveniently carried out by catalytic hydrogenation in the presence of a noble metal catalyst such as palladium at low pressure, for example 1—5 atmospheres.

Compounds I and IV, can be readily converted to the corresponding acyl derivatives by reaction with suitable acylating agents. The acylated derivatives thus obtained are useful products which are valuable means of identifying and further purifying the chroman compounds. In addition, the acylated derivatives are useful since they are less sensitive to oxygen and peroxide and hence can be stored for longer periods of time without deterioration. Although any of the various acyl derivatives can be used, the acyl derivatives of carboxylic acids having from 1 to 9 carbon atoms are especially useful, and these acyl compounds represent preferred embodiments of the present invention. These acylated compounds are readily prepared by reacting the chromans with the appropriate carboxylic acid chlorides or anhydrides, preferably in the presence of a suitable base such as pyridine or a complex-forming agent. The acylated chromans are readily reconverted to the corresponding chromans by mild acid hydrolysis or by reaction with lithium aluminium hydride or Grignard reagent.

The chromans of the present invention have been found to be useful antioxidants which can be used to inhibit the oxidation of various animal and vegetable fats and oils. These chromans can be used either by themselves or in combination with other antioxidant materials which are known in the art as antioxidants.

The following examples are given to illustrate the procedures for the preparation of the compounds of the present invention:

EXAMPLE I.

Production of the chroman of coenzyme $Q_{10}$ from the quinone (coenzyme $Q_{10}$, II) is carried out as follows:

29 mg. of coenzyme $Q_{10}$ was placed in a 10 mm. tube closed at one end and evacuated on a mercury vapour pump to 1—10 microns pressure. The tube was heated around the sample. At 250—280° a light yellow distillate (oil) was collected in the cool portion of the tube. This distillate was the chroman, i.e. 2,5-dimethyl-2-[3¹-methyl-2¹-butenyl - octakis - (3¹ - methyl - 2¹ - butenylene) - methyl] - 6 - hydroxy - 7,8 - dimethoxy-chroman (Ia). In the infra-red region it showed the absorption bands expected of such a formula as follows (Solvent, carbon tetrachloride):

| Band | Structural Indication |
|---|---|
| 2.70 $\mu$ | —OH |
| — | C=O absent |
| 6.65 $\mu$ | phenyl |

Spectrum similar to that of $\alpha$-tocopherol.

EXAMPLE II.

Preparation of the chroman of coenzyme $Q_{1_0}$ from the hydroquinone of coenzyme $Q_{10}$:

The hydroquinone of coenzyme $Q_{1_0}$ (III) was prepared from the quinone by dissolving 100 mg. of coenzyme $Q_{10}$ (II) in ethanol and adding excess of sodium borohydride as an aqueous solution; this completely removed the original yellow-orange colour. The solution was diluted with two volumes of water and extracted three times with petroleum ether. The petroleum ether extracts were washed with water, dried over magnesium sulphate, filtered and evaporated under vacuum to a residual oil, (the product is protected from air oxidation throughout by an atmosphere of nitrogen or carbon dioxide). When pumped free of residual solvent, the oil crystallized. (From the crystalline residue, the pure hydroquinone of coenzyme $Q_{10}$ (III) may be recrystallized from alcohol-petroleum ether mixtures m.p. 47°). This hydroquinone is used, however, as the residue obtained directly from solvent extraction; this is dissolved in methanol-benzene solution (3 : 1, approximately 40 ml.), to this is added 1 to 2 ml. of concentrated aqueous hydrochloric acid, and the mixture is refluxed under a protective atmosphere for eight hours.

The solution is cooled, diluted with two volumes of water, extracted three times with petroleum ether, and the extract is washed with water, dried over magnesium sulphate, filtered and concentrated under vacuum, leaving approximately 0.9 g. of an oily residue of the chroman of coenzyme $Q_{10}$; the infra-red spectrum of this material shows it to be substantially identical with the chroman of coenzyme $Q_{1_0}$ produced as in Example I.

EXAMPLE III.

Acetylation of the Chroman from coenzyme $Q_{10}$:

Approximately 200 mg. of the chroman from coenzyme $Q_{10}$, prepared as examplified in Examples I and II, was treated with a mixture of 1 ml. of acetic anhydride and 3 ml. of anhydrous pyridine; the resulting reaction mixture was heated for one hour at 60° C.

The acetate thus formed was obtained by diluting the reaction mixture with 2 volumes of water and extracting with ether. The ether extract was washed successively with dilute hydrochloric acid, water, 10% sodium bicarbonate solution and water. The ether extract was dried over magnesium sulphate, filtered and evaporated at reduced pressure.

This residual acetate (i.e. 2,5-dimethyl-2-[3¹-methyl-2¹-butenyl-octakis-(3¹-methyl-2¹-butenylene)-methyl]-6-acetoxy-7,8-dimethoxy-chroman (1b) was a light yellow oil. In isooctane solution the sample showed an ultraviolet absorption band at 282 mμ; $E^{1\%}_{1cm} = 20.4$.

EXAMPLE IV.

Preparation of the *p*-nitrobenzoate of the chroman of coenzyme $Q_{1_0}$:

Approximately 100 mg. of the chroman of coenzyme $Q_{1_0}$ (I) produced as exemplified in Examples I and II was treated with 100 mg. of *p*-nitrobenzoyl chloride and 2 ml. of dry pyridine at 100° for one hour.

The reaction mixture was diluted with 2 volumes of water and extracted with ether. The ether extract was washed successively with dilute hydrochloric acid, water, 10% sodium bicarbonate solution and water. It was dried over magnesium sulphate, filtered, and the ether evaporated at reduced pressure.

The residual *p*-nitrobenzoate of the chroman, i.e. 2,5-dimethyl-2-[3¹-methyl-2¹-butenyl - octakis - (3¹ - methyl - 2 - butenylene) - methyl] - 6 - *p* - nitrobenzyloxy - 7,8-dimethoxy-chroman (Ic), was crystallized from ethanol or from a mixture of acetone and petroleum ether, m.p. about 112°.

The infrared spectrum was observed in carbon tetrachloride solution:

| Band | Structural Indications |
|---|---|
| 5.71 μ | carbonyl (ester) |
| 6.17 μ | phenyl |
| 6.48 μ., 7.39 μ | nitro |
| 9 μ region | —C—O—C— |
| | No —OH band |

The ultraviolet absorption spectrum was observed in isoctane and showed a strong band at 255 mμ., $E^{1\%}_{1\,cm.}$ =278, inflections at 290 mμ., $E^{1\%}_{1\,cm.}$ =62.2 and 305 mμ., $E^{1\%}_{1\,cm.}$ =36.6.

EXAMPLE V.

Hydrogenation of the chroman from coenzyme $Q_{10}$:

A solution of 100 mg. of the chroman from coenzyme $Q_{10}$, prepared as exemplified in Examples I and II, is made in 50 ml. of ethanol (free of benzene, for catalytic use), approximately 100 mg. of 5% palladium (on charcoal support) catalyst is added, and the mixture is agitated with hydrogen gas under one to 3 atmospheres pressure for three to five hours at room temperature until absorption is essentially complete. The catalyst is removed by filtration and the filtrate is concentrated under vacuum and pumped free of residual solvent. The residual, essentially colourless, oil is substantially pure 2,5-dimethyl - 2 - ($4^1$,$8^1$,$12^1$,$16^1$,$20^1$,$24^1$,$28^1$,$32^1$,$36^1$ - nonamethyl - heptatricontanyl) - 6-hydroxy - 7,8 - dimethoxy - chroman (IVa) as shown by the absence of bands for olefinic (—CH=) protons in the nuclear magnetic resonance spectrum.

EXAMPLE VI.

By treatment of 100 mg. of the hydrogenated chroman, obtained according to the method illustrated in Example V, with 0.5 ml. of acetic anhydride and 1.5 ml. of anhydrous pyridine according to the method of Example III, the acetate of the hydrogenated chroman (IVb, i.e. 2,5 - dimethyl - 2 - [$4^1$,$8^1$,$12^1$,$16^1$,$20^1$,$24^1$,$28^1$,$32^1$,$36^1$-nonamethyl - heptatricontanyl] - 6 - acetoxy - 7,8 - dimethoxy - chroman), is obtained as a colourless oil.

EXAMPLE VII.

A solution of 100 mg. of coenzyme Q in about 5 ml. of glacial acetic acid was heated to boiling under a reflux condenser and sufficient stannous chloride added to decolorize the solution. The heating under reflux was continued for about 15 minutes. The acetic acid was then evaporated at reduced pressure and the resulting residue was extracted with ether. The ether layer was washed repeatedly with water, dried over magnesium sulphate and then evaporated to obtain the chroman, 2,5-dimethyl-2-[$3^1$-methyl-$2^1$ - butenyl - octakis - $3^1$ - methyl - $2^1$ - butenylene) - methyl] - 6 - hydroxy - 7,8 - dimethoxychroman, in nearly pure form of a light yellow oil. Small traces of impurities can be removed by counter-current extraction using a mixture of hexane and dimethylformamide as the solvent.

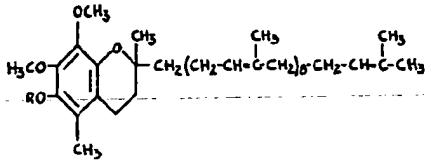
The new chromans of the present invention are useful antioxidants which can be used to inhibit the oxidative rancidity which occurs during the storage and handling of oleaginous materials such as vegetable and animal oils and fats. Thus, the addition of amounts of 0.05 to about 0.1% of these chromans will inhibit the formation of peroxides which is indicative of the occurrence of rancidity. For example, the antioxidant properties of the chromans in inhibiting the oxidative rancidity of corn oil by the modified Schoal test is carried out as follows:

Corn oil (obtained without any commercially added antioxidants, and free of corn germ oil) is added to a 100 ml. beaker until a weight of 50 g. of said oil has been introduced. One beaker, so filled is used as a control; other beakers of the same size and type are filled with the same amount of corn oil, one being provided for each sample or mixture to be tested. To the test beakers, taken individually, are added suitable amounts of the individual sample to be tested; in the case of the chroman of Coenzyme of Q—10 0.05% to 0.1% is added and mixed well with the corn oil.

All beakers are then heated in a thermostatically controlled bath at 62° C. for six days. At the end of four, five, and six days, aliquots of 5 ml. are withdrawn from each beaker. Each aliquot is mixed with 30 ml. of glacial acetic acid-chloroform solution (6:4) and to each of the resulting solutions, an 0.5 ml. portion of saturated potassium iodide solution (in water) is added with good mixing until clear. The brownish colour developed in each tube is compared with standards of the Master Colour Series. It will be noted that colour develops soonest in the control, and 2 or more days of additional heating is required for samples containing antioxidants.

WHAT WE CLAIM IS:—

1. A chroman compound of the formula:



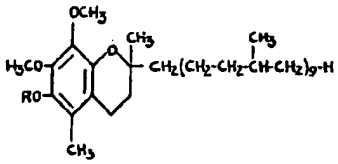
where R is a hydrogen atom or an acyl radical.

2. A compound as claimed in Claim 1, in which R represents an acyl radical derived from a carboxylic acid having from 1 to 9 carbon atoms in the molecule.

3. A compound as claimed in Claim 2, in which R represents acetyl.

4. A chroman compound having the formula of Claim 1, in which R represents *p*-nitrobenzoyl.

5. A chroman compound of the formula:

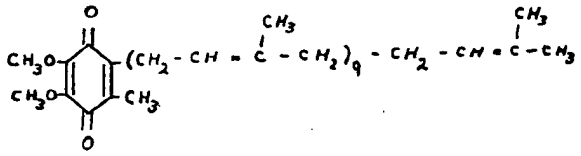


where R is as defined in Claim 1.

6. A compound as claimed in Claim 5 in which R represents an acyl radical derived from a carboxylic acid having from 1 to 9 carbon atoms in the molecule.

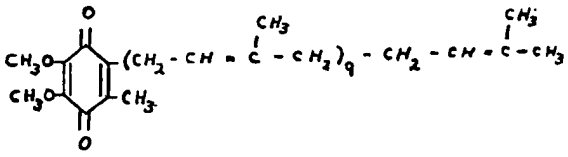
7. A compound as claimed in Claim 6, in which R represents acetyl.

8. A process for producing a chroman of Coenzyme $Q_{10}$ which comprises heating a compound having the formula:



to effect internal cyclization and thereby obtain the compound claimed in Claim 1, where R is a hydrogen atom.

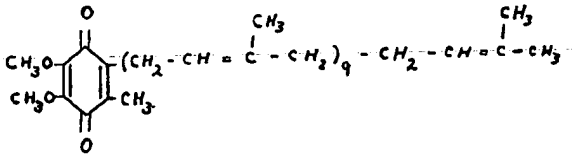
9. The process for producing a chroman compound which comprises reducing a quinone compound of the formula:



to the corresponding hydroquinone, and heating this hydroquinone in the presence of an acid catalyst to produce the chroman compound claimed in Claim 1, where R is a hydrogen atom.

10. A process as claimed in Claim 9, in which the reduction of the quinone to the hydroquinone is carried out with sodium borohydride.

11. A process for producing a chroman compound which comprises reacting a quinone compound of the formula:



with stannous chloride at a temperature in excess of about 50° C. to produce a compound as claimed in Claim 1, where R is a hydrogen atom.

12. A process as claimed in claim 11, in which the reaction is carried out in glacial acetic acid at a temperature of about 100° C.

13. The process which comprises reacting the compound as claimed in claim 2 or 6 where R is a hydrogen atom, with an acylating agent to produce the corresponding acylated derivative.

14. The process which comprises reducing the compound claimed in claim 1 where R is a hydrogen atom to produce a compound as claimed in claim 5, where R is a hydrogen atom.

15. A process as claimed in claim 8, substantially as hereinbefore described in Example I.

16. A process as claimed in claim 9, substantially as hereinbefore described in Example II.

17. A process according to claim 11, substantially as hereinbefore described in Example VII.

18. A process as claimed in claim 13, substantially as hereinbefore described in any one of Examples III, IV, or VI.

19. A process as claimed in claim 14, substantially as hereinbefore described in Example V.

20. A compound as claimed in claim 1 or 5, when prepared by a process as claimed in any one of claims 8 to 19.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 Staple Inn, London, W.C.1.

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